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Familial Mediterranean Fever: A Comprehensive Review of Pathogenesis, Genetics, and Epigenetic Regulation

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Familial Mediterranean Fever (FMF) is the first described and most prevalent monogenic autoinflammatory periodic fever syndrome worldwide. The disease is caused by pathogenic variants in the *MEFV* (Mediterranean fever) gene, which lead to dysregulated innate immune responses and a persistent hyperinflammatory state. Despite extensive genetic characterization, the molecular mechanisms linking *MEFV* mutations to aberrant inflammation remain incompletely understood. Moreover, substantial clinical heterogeneity—manifested as incomplete penetrance, variable expressivity, and modulation by additional autoinflammatory genes—indicates that FMF pathogenesis extends beyond classical Mendelian inheritance. Emerging evidence suggests that epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA regulation, may contribute to phenotypic variability, disease severity, and therapeutic response; however, available data are limited and occasionally conflicting. This review provides a comprehensive and up-to-date overview of the genetic, molecular, and epigenetic factors implicated in FMF, highlights unresolved controversies, and proposes future research priorities aimed at elucidating disease mechanisms and improving clinical management.

INTRODUCTION

Familial Mediterranean Fever (FMF) is a monogenic autoinflammatory disorder predominantly affecting individuals of Mediterranean descent, including Turks, Armenians, Arabs, and non-Ashkenazi Jews.[1] It is the most common hereditary periodic fever syndrome worldwide and is characterized by recurrent episodes of fever, serositis, and arthritis (Figure 1). Among its complications, AA amyloidosis is the most serious and represents the leading cause of mortality in FMF patients. Daily prophylactic administration of colchicine remains the cornerstone of treatment, effectively preventing the development of amyloidosis.[2]

Pathogenic variants in the *MEFV* gene play a central role in FMF pathogenesis. This gene encodes pyrin, a protein critical for regulating the inflammatory response by modulating the inflammasome complex.[2,3] Despite extensive research, the precise mechanisms underlying pyrin inflammasome overactivation in FMF remain incompletely understood.

This review provides an updated and comprehensive overview of the genetics, epigenetics, and pathogenesis of FMF.

FMF results from pathogenic variants in the *MEFV* gene, which encodes the pyrin protein.[4,5] These variants lead to a gain-of-function effect in pyrin.[6] Pyrin functions as an inflammasome-forming protein.[7]

Inflammasomes are multiprotein complexes that play a critical role in the innate immune response to pathogens.[8] Unlike the adaptive immune system, the innate immune system does not recognize pathogen-specific molecules; instead, it detects conserved molecular patterns shared by pathogens—pathogen-associated molecular patterns (PAMPs)—or alterations arising from cellular damage, known as damage-associated molecular patterns (DAMPs).[9] By monitoring the cytosol, inflammasomes trigger an inflammatory response upon detection of PAMPs or DAMPs.[10]

One notable inflammasome is the pyrin inflammasome. Because pyrin inflammasome overactivation underlies FMF pathogenesis, this review first summarizes its structure, function, and activation, along with recent advances in the field. Subsequently, we examine the pyrin inflammasome specifically in patients with FMF, highlighting emerging findings and hypotheses that provide new insights into disease pathophysiology. This discussion is followed by an overview of

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the intriguing relationship between FMF and *Yersinia*, a connection that has reshaped current understanding of FMF epidemiology and biology. Finally, we address the genetic landscape of FMF and explore epigenetic regulatory mechanisms that may contribute to phenotypic variability.

PYRIN INFLAMMASOME

Structure

The basic structure of an inflammasome consists of a sensor that detects pathogenic insults, an adaptor protein that bridges the sensor and the executioner, and an executioner that initiates the inflammatory cascade.[11] In the pyrin inflammasome, these components correspond to pyrin (sensor), [apoptosis-associated (ASC) speck-like protein containing a caspase recruitment domain (CARD)] (adaptor), and caspase-1 (executioner), respectively.

Pyrin, also known as tripartite motif–containing protein 20 or marenostrin, is a pattern recognition receptor that monitors cytosolic homeostasis and senses alterations within the cytosol, referred to as homeostasis-altering molecular processes.[12] Structurally, pyrin comprises an N-terminal pyrin domain (PYD), a zinc finger domain (B-box), a central helical scaffold (CHS), and a C-terminal B30.2 domain (Figure 2).[13,14]

The PYD domain of pyrin interacts with the PYD domain of ASC, promoting ASC oligomerization. Oligomerized ASC subsequently engages procaspase-1 via its CARD domain, leading to autocatalytic cleavage and activation of caspase-1.[15]

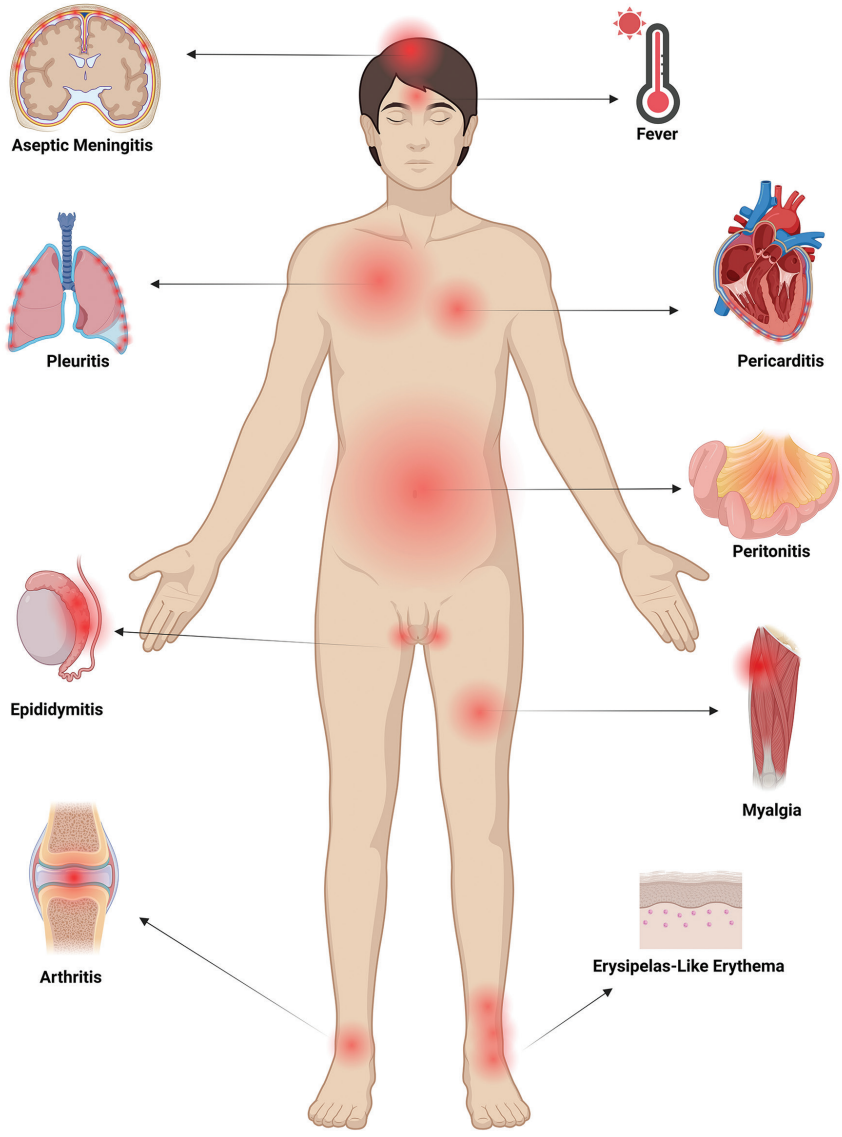

FIG. 1. Clinical features of Familial Mediterranean Fever.
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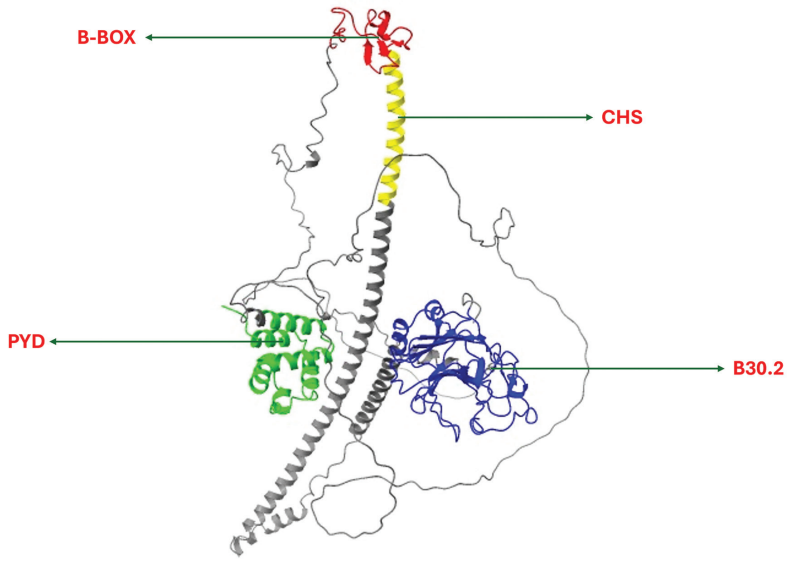

FIG. 2. Pyrin protein structure.

The structure of pyrin protein with highlighted subdomains is illustrated. The part highlighted with green indicates PYD domain, which is encoded by Exon-3. The part highlighted with yellow illustrates CHS domain, which is encoded by Exon-6. The part highlighted by red demonstrates B-box domain, which is encoded by Exon-2. The part highlighted with blue indicates B30.2 domain, which is encoded by Exon-10. PYD, pyrin domain; CHS, central helical scaffold; B-box, zinc finger domain.

Function and activation

The activation of the pyrin inflammasome under physiological conditions is illustrated in Figure 3.

Under normal conditions, pyrin remains in an inactive state, which is maintained by the small GTPase RhoA.[7] RhoA functions as a "guard" of the pyrin inflammasome.[7] Rather than interacting directly with pyrin, RhoA inhibits inflammasome activation through the serine–threonine protein kinases PKN1 and PKN2.[16] Specifically, RhoA activates PKN1 and PKN2, which then bind to pyrin and phosphorylate serine residues at positions 208 and 242.[16,17] This phosphorylation facilitates the binding of the 14-3-3 chaperone to pyrin, thereby preventing pyrin inflammasome activation.[16]

Bacteria and bacterial toxins, such as the clostridial toxin TcdB, can alter RhoA activity, effectively "disarming" this regulatory guard.[7] This disruption reduces pyrin phosphorylation and the binding of 14-3-3 proteins to pyrin.[7] The decreased association of 14-3-3 proteins relieves pyrin inhibition, leading to activation of the pyrin inflammasome. This mechanism represents the primary pathway through which the pyrin inflammasome senses bacterial toxins and homeostatic disturbances.[16]

Upon activation, pyrin interacts with ASC via homotypic PYD–PYD interactions, promoting ASC oligomerization.[16,18] The CARD domain of oligomerized ASC then stimulates autocatalytic cleavage of procaspase-1 into active caspase-1, the principal executioner of inflammasome-induced inflammatory responses. Active caspase-1 cleaves proinflammatory cytokines interleukin (IL)-1β and IL-18 into their mature forms, triggering an exaggerated immune response largely mediated by neutrophils.[19,20]

In addition to cytokine activation, caspase-1 cleaves the pore-forming protein Gasdermin-D, producing its active form and inducing inflammatory cell death, known as pyroptosis.[21] Enhanced pyroptosis further amplifies inflammation by promoting the release of cytokines and alarmins such as S100A8/A9 and S100A12.[22] Recent studies have also demonstrated that neutrophil extracellular traps are formed as a consequence of heightened neutrophil activation in patients with FMF.[23]

PYRIN INFLAMMASOME IN FAMILIAL MEDITERRANEAN FEVER

Figure 4 summarizes the current understanding of the pyrin inflammasome in FMF. Despite advances in elucidating pyrin inflammasome activation and downstream signaling, the precise mechanisms underlying its overactivation in patients with FMF remain incompletely understood.[7,16] Current evidence suggests the involvement of distinct yet interconnected regulatory nodes, including the B30.2 domain, cytoskeletal dynamics, and autophagic pathways.[12,24,25]

Structural regulation: the B30.2 and central helical scaffold domains

Most FMF-causing variants are located in exon 10 of the *MEFV* gene, which encodes the B30.2 domain of pyrin.[13] Although the precise role of the B30.2 domain in pyrin inflammasome activation remains unclear, Weinert et al.[24] identified a shallow cavity containing hydrophobic clusters within B30.2, which they proposed as a potential ligand-binding site. They further observed that approximately two-thirds of pathogenic variants in the B30.2 coding region cluster near this cavity, suggesting that these variants likely alter its ligand-binding activity.[24]

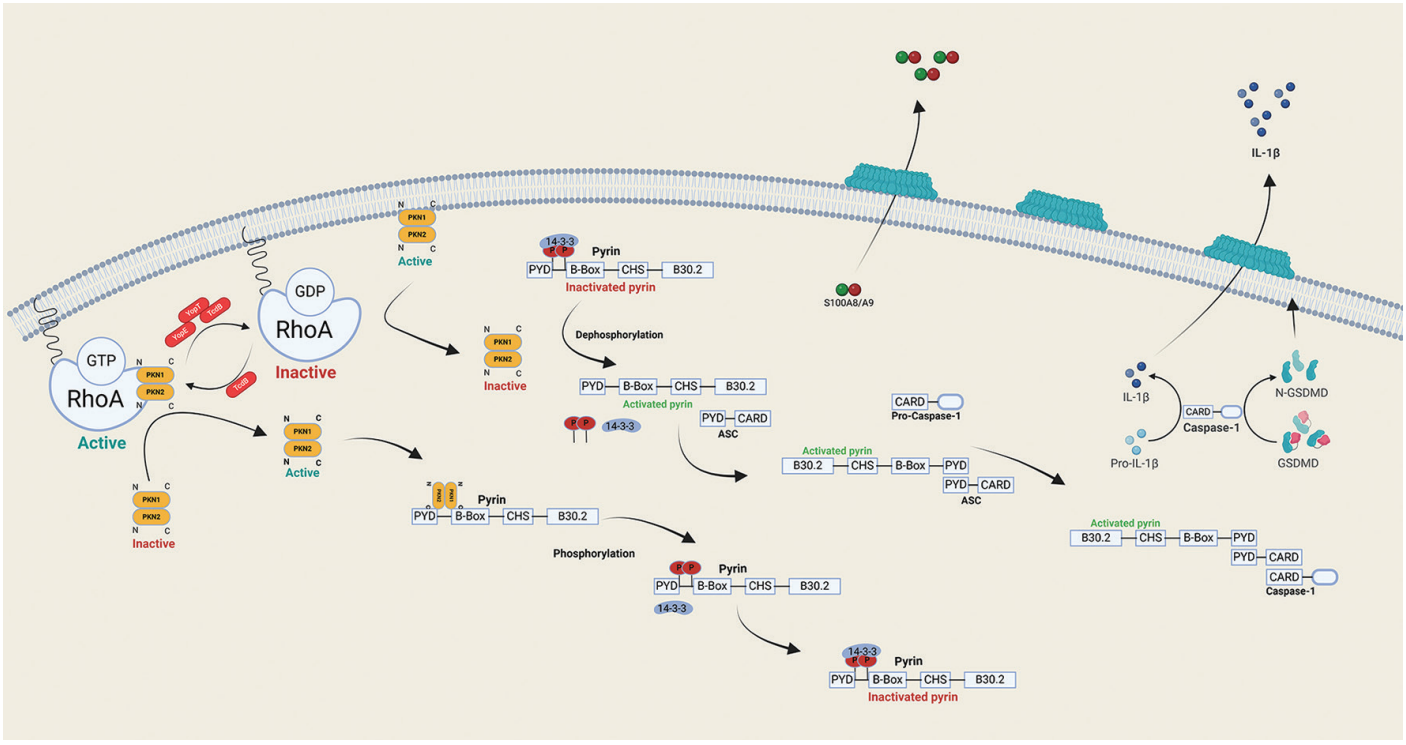

FIG. 3. Pyrin inflammasome activation under physiological conditions.

Under normal conditions, RhoA acts as a guard of pyrin inflammasome. RhoA activates PKN1 and PKN2 which phosphorylate pyrin at serine residues 242 and 208 located between PYD and B-Box. Phosphorylated pyrin has a higher affinity for chaperone protein 14-3-3 and binds it, resulting in inactivation of pyrin inflammasome. In pathogenic conditions where there is a toxin release or disruptions in the cytosolic homeostasis, RhoA gets inactivated and PKNs cannot be activated, preventing pyrin phosphorylation. Dephosphorylated pyrin does not bind 14-3-3 and remains active. Activated pyrin interacts with ASC through its PYD domains, leading to ASC oligomerization. Oligomerized ASC interacts with procaspase-1 through its CARD domains, resulting in the activation of procaspase-1 to caspase-1. Activated caspase-1 cleaves proinflammatory cytokines and GSDMD to their active forms. Activated GSDMD forms pores on the cellular membrane through which the proinflammatory cytokines and alarmins (S100A8/A9) are released. Created in BioRender.com. PYD, pyrin domain; B-box, zinc finger domain; GSDMD, gasdermin-D.

Chae et al.[25] and Arakelov et al.[26] reported that the B30.2 domain directly interacts with caspase-1, exerting an inhibitory effect on its activation. Studies indicate that FMF-causing variants in B30.2 weaken this interaction, thereby relieving caspase-1 inhibition.[27] Another study demonstrated that β2-microglobulin binds the B30.2 domain and promotes inflammasome activation, leading to caspase-1 activation.[28] This study also identified a negative feedback mechanism mediated by the p20 subunit of caspase-1, which binds B30.2 and reduces pyrin's interaction with β2-microglobulin. FMF-associated MEFV variants were shown to diminish this inhibitory effect, contributing to enhanced inflammasome activation.[28]

Recently, Chirita et al.[14] demonstrated that the B30.2 domain is dispensable for pyrin activation. Instead, it negatively regulates pyrin activation, acting downstream of pyrin dephosphorylation and upstream of ASC speck oligomerization.[14] Weinert et al.[24] showed that the remaining one-third of B30.2 variants cluster opposite the peptide-binding cavity. They hypothesized that these variants alter the spatial orientation between B30.2 and the central coiled-coil domain (a subdomain of CHS) and subsequently confirmed this hypothesis in a follow-up study.[29] Chirita et al.[14] further demonstrated that variants in exons 3–8, which encode the CHS domain, mimic the effects of FMF-causing B30.2 variants. They also proposed that CHS and B30.2 function together to negatively regulate caspase-1 activation.[14]

Taken together, these findings suggest that B30.2 acts as a negative regulator of pyrin inflammasome activation in coordination with CHS. FMF-causing pathogenic variants located in exons 10 and 3–8 disrupt this inhibitory mechanism, resulting in pyrin inflammasome overactivation. Although the negative regulatory roles of B30.2 and CHS have been demonstrated, the precise molecular mechanisms remain unclear. Elucidating this regulation is of critical importance, as it may enhance understanding of FMF pathogenesis and inform the development of novel therapeutic strategies.

Cytoskeletal regulation and motility

Colchicine, the primary treatment for FMF, is well known for its effects on the cytoskeleton, prompting researchers to investigate the potential role of cytoskeletal dynamics in FMF pathogenesis. Figure 5 illustrates cytoskeletal organization in FMF. The pyrin inflammasome has long been recognized to associate with cytoskeletal components.

In 2001, Mansfield et al.[30] demonstrated that pyrin colocalizes with microtubules and the actin cytoskeleton via its N-terminal

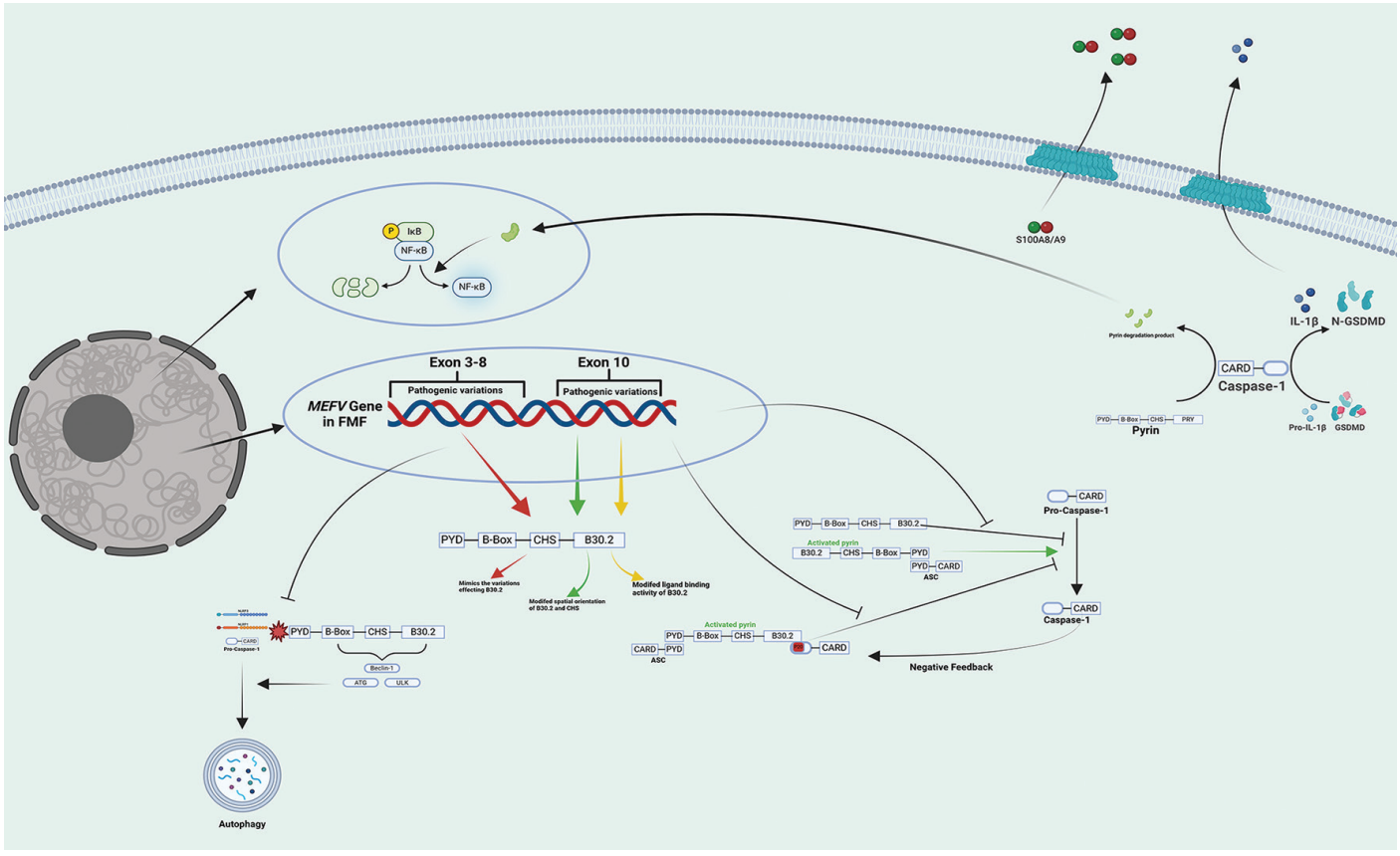

FIG. 4. Pyrin inflammasome in FMF.

Some of the pathogenic variations (yellow arrow) occurring in the Exon-10 of MEFV gene modifies the ligand binding activity of B30.2, while some (green arrow) of them modify the spatial orientation of B30.2 with CHS. On the other hand, pathogenic variations occurring in the Exon-3-8, which encodes CHS mimic the variations occurring in the Exon-10. B30.2 has a direct inhibitory effect on caspase-1 activation, which is removed by FMF-causing pathogenic variations. P20 subdomain of caspase-1 directly interacts with B30.2, resulting in inhibition of caspase-1 activation and leads to a negative feedback mechanism. This negative feedback is removed by FMF-causing pathogenic variations. Pyrin itself can be a substrate and cleaved by caspase-1. The degradation products of pyrin stimulate the degradation of IkB complex to NFkB, further exacerbating the inflammatory situation. Pyrin interacts with certain inflammasome products thorough PYD domain and with autophagy drivers, acting like a receptor of autophagy. This activity is also disrupted by FMF-causing pathogenic variations. Created in BioRender.com. PYD, pyrin domain; CHS, central helical scaffold; B-box, zinc finger domain; FMF, Familial Mediterranean Fever.

domain. Subsequently, Shoham et al.[31] reported that pyrin interacts with proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1), a regulator of cytoskeletal organization. In addition to its role in cytoskeletal regulation, PSTPIP1 binds the B-box domain of pyrin, promoting pyrin activation downstream of dephosphorylation and upstream of ASC oligomerization.[32]

In 2016, Van Gorp et al.[33] and Gao et al.[34] confirmed that pyrin interacts with microtubules and demonstrated that an intact microtubular network is essential for both pyrin dephosphorylation and subsequent activation of the pyrin inflammasome. They[33,34] further showed that microtubules function downstream of pyrin dephosphorylation and upstream of ASC oligomerization. Moreover, Van Gorp et al.[33] and Magnotti et al.[35] reported that, although FMF-associated pathogenic variants do not disrupt the physical interaction between pyrin and microtubules, these variants circumvent the requirement for an intact microtubular system in pyrin inflammasome activation.

Recently, CDC42 (cell division cycle 42), a well-established regulator of the cytoskeleton[36,37] was identified as a critical component of the pyrin pathway. Mechanistically, CDC42 promotes microtubule-dependent pyrin assembly, acting downstream of pyrin dephosphorylation and upstream of ASC oligomerization.[38,39] The essential role of CDC42 in FMF pathogenesis is further supported by evidence showing that CDC42 deletion prevents inflammatory cell death in disease models.[39]

Furthermore, pyrin inflammasome activation appears to regulate inflammatory cell migration. Several studies have shown that pyrin colocalizes with polymerizing actin at the leading edge of migrating monocytes.[40,41] The functional significance of this interaction is underscored by pyrin knockdown models, which exhibit impaired migratory capacity.[41] Recently, Akbaba et al.[42] reported that pyrin inflammasome activation specifically enhances inflammatory cell migration in FMF patients, distinguishing them from patients with cryopyrin-associated periodic syndromes (CAPS) and healthy controls.

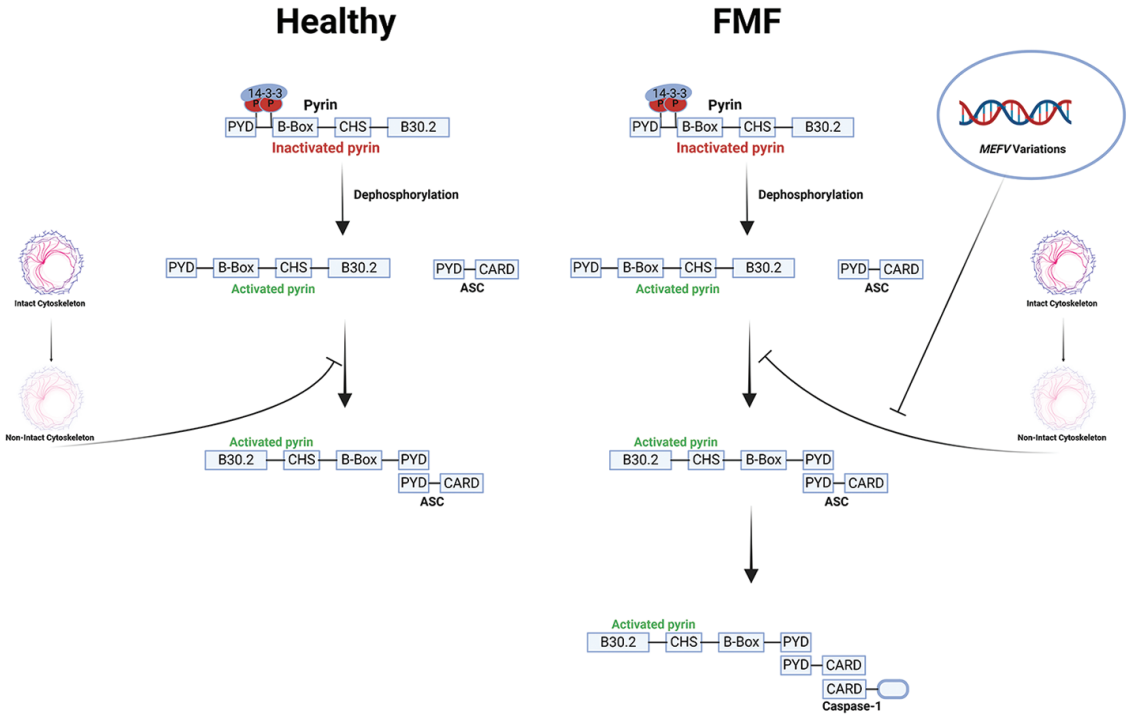

FIG. 5. Cytoskeleton in the pathogenesis of FMF.

Studies have shown that cytoskeleton is involved in the regulation of pyrin inflammasome activation downstream of dephosphorylation and upstream of ASC oligomerization, and an intact cytoskeleton is required for activation. Therefore, disruption of cytoskeleton blocks the activation of pyrin inflammasome. On the other hand, the need for an intact cytoskeleton for pyrin inflammasome activation is removed in patients with FMF. Thus, pyrin inflammasome activation occurs even in the presence of a disrupted cytoskeleton. Created in BioRender. com. PYD, pyrin domain; CHS, central helical scaffold; B-box, zinc finger domain; FMF, Familial Mediterranean Fever.

Alternative regulatory mechanisms

Chae et al.[43] demonstrated the involvement of the NF-κB pathway in FMF pathogenesis. Their study[43] revealed that pyrin can serve as a substrate for caspase-1, and the cleavage product of pyrin translocates to the nucleus, where it enhances NF-κB activity by promoting IκB degradation. Additionally, caspase-1–mediated pyrin cleavage was found to be elevated in FMF patients. These observations were corroborated by Fayez et al.,[27] whose *in silico* analysis of pyrin and caspase-1 supported the findings of Chae et al.[43]

Another regulatory mechanism affected by disease-causing MEFV variants is pyrin-mediated autophagy. Kimura et al.[44] demonstrated that pyrin functions as an autophagy receptor, recognizing and promoting the autophagy of NOD-like receptor pyrin domain–containing 1 (NLRP1), NOD-like receptor pyrin domain–containing 3 (NLRP3), and pro–caspase-1. Pathogenic MEFV variants were associated with reduced autophagy of these inflammasome components. Consistent with these findings, Skendros et al.[45] and Mitroulis et al.[46] reported diminished autophagy of inflammasome components in FMF patients.

Mortensen et al.[47] demonstrated that pyrin inflammasome activation reduces the secretion of IL-1 receptor antagonist, thereby diminishing anti-inflammatory capacity and suggesting a novel mechanism contributing to FMF pathogenesis.

Integrated model of pathogenesis

Collectively, current evidence suggests that B30.2/CHS dysregulation, cytoskeletal alterations, and impaired autophagy converge on a common pathogenic node: the loss of negative regulation between pyrin dephosphorylation and ASC oligomerization. Because the cytoskeleton modulates pyrin activation at the same step as the B30.2 and CHS domains (downstream of dephosphorylation), we propose a functional coupling between these systems. Specifically, the B30.2 domain likely depends on precise cytoskeletal configurations to exert its inhibitory effect. FMF-associated variants impair B30.2/CHS function and disrupt this cytoskeleton-dependent regulation. In combination with reduced autophagic clearance, these defects lower the activation threshold of the pyrin inflammasome, promoting excessive ASC oligomerization and driving the hyperinflammatory phenotype observed in FMF.

FAMILIAL MEDITERRANEAN FEVER AND *YERSINIA*

Pyrin functions as a pattern recognition receptor that senses perturbations in cellular homeostasis, including those induced by microbial processes.[12] Studies have shown that various bacterial toxins modulate pyrin inflammasome–mediated immune responses by targeting Rho GTPases.[7] Notable toxins that regulate this guard mechanism and thereby influence pyrin inflammasome activation include the T6SS of *Burkholderia cenocepacia*;[7,19,48] TcdA and TcdB of *Clostridium difficile*;[7,49] VopS of *Vibrio parahaemolyticus*;[7] and YopE, YopT, and YopM of *Yersinia pestis*.[50,51] Among these, *Y. pestis* holds particular significance.

Toxins produced by *Y. pestis* differentially regulate the pyrin inflammasome. YopE and YopT inhibit Rho GTPases, thereby disrupting phagocytosis[52] and activating the pyrin inflammasome.[50,53-55] In contrast, YopM exploits RhoA-activated kinases to phosphorylate pyrin, suppressing pyrin inflammasome–mediated inflammatory responses.[50,51,56,57]

For decades, researchers have sought to explain the high carrier frequency of FMF-associated variants among Mediterranean populations, interpreting it as a possible outcome of selective advantage against a historical disease.[58,59] *Y. pestis*, the plague-causing bacterium, has emerged as a plausible driver of positive selection in FMF carriers for several reasons:

Y. pestis suppresses pyrin inflammasome–mediated inflammation via YopM.[50,51,56,57]

FMF-associated variants confer a gain of function, resulting in overactivation of the pyrin inflammasome.[6]

Historical plague epidemics were widespread throughout the Mediterranean region.[60]

In 2020, Park et al.[61] provided strong evidence supporting this hypothesis. Their key findings were:

Haplotype analysis indicated recent positive selection of FMF-associated variants in the studied population.

Mutant pyrin exhibited reduced binding affinity to YopM compared with wild-type pyrin.

FMF patients mounted a stronger immune response against *Y. pestis* than healthy individuals.

Other microorganisms, including *Mycobacterium tuberculosis*[62] and *Brucella melitensis*,[63] have also been proposed as contributors to the positive selection of FMF variants; however, the evidence supporting these claims remains limited.

GENETICS OF FAMILIAL MEDITERRANEAN FEVER

The MEFV gene and inheritance patterns

FMF is an autoinflammatory disorder caused by pathogenic variants in the *MEFV* gene. The causative locus for FMF was first identified in 1997 by the International FMF Consortium and the French FMF Consortium.[4,5] The *MEFV* gene encodes pyrin, a protein that regulates the inflammasome and IL-1β processing, directly linking *MEFV* variants to innate immune dysregulation. Since its discovery, *MEFV* has remained one of the most extensively studied autoinflammatory genes for elucidating mechanisms of dysregulated innate immunity.[64]

Historically, FMF has been considered an autosomal recessive disorder. Biallelic pathogenic *MEFV* variants, particularly prevalent in populations such as Turks, Armenians, Arabs, and non-Ashkenazi Jews,[65] are strongly associated with disease. However, clinical penetrance is incomplete, and heterozygous carriers may also manifest typical FMF phenotypes, suggesting a spectrum between recessive and dominant-like inheritance patterns.[66] Recent evidence supports a continuum of inheritance mechanisms, influenced by variant-specific functional effects as well as genetic and environmental modifiers. This incomplete penetrance and variable expressivity are particularly evident when comparing FMF phenotypes across diverse geographic and ethnic backgrounds.

Variant spectrum and genotype–phenotype correlations

The *MEFV* gene exhibits extensive genetic variability, with over 400 variants currently cataloged in Infevers.[67] However, only a small subset of these variants accounts for the majority of FMF cases. The most frequent and clinically significant variants are p.M694V, p.V726A, and p.M680I. Among them, p.M694V is consistently associated with early-onset disease, severe clinical phenotype, colchicine resistance, and a high-risk of amyloidosis. In contrast, p.V726A and p.M680I, although enriched in Mediterranean populations, are generally linked to milder phenotypes compared with p.M694V.[65]

Variants such as p.E148Q and p.R202Q have recently been reclassified as low-penetrance or likely benign, with expert consensus groups advising against their reporting as pathogenic in clinical settings. Large-scale cohort studies continue to confirm that genotype remains the strongest predictor of disease severity, although environmental and epigenetic factors also modulate clinical outcomes.

Genetic complexity: modifiers, epigenetics, and overlap

Beyond inheritance patterns, the genotype–phenotype relationship in FMF has garnered considerable attention due to its role in explaining the clinical complexity and heterogeneity of the disease. Patients carrying identical *MEFV* variants, particularly those with low penetrance, may exhibit a wide spectrum of disease courses, ranging from subclinical carriers to severe, colchicine-resistant FMF. This heterogeneity is partially attributable to the influence of modifier genes and environmental factors. Among genetic modifiers, polymorphisms in *SAA1* have been strongly associated with an increased risk of amyloidosis.[68,69] In addition, recent studies have highlighted the contribution of epigenetic mechanisms, including DNA methylation and non-coding RNA regulation, in modulating pyrin inflammasome activity and *MEFV* expression.[70]

Further complexity arises from the clinical and genetic overlap between FMF and other monogenic autoinflammatory diseases. In FMF-prevalent regions, particularly Türkiye, individuals clinically diagnosed with FMF but lacking biallelic *MEFV* variants have been

found to carry pathogenic variants in other autoinflammatory genes. For example, Karacan et al.[71] reported families with FMF-like phenotypes harboring either a homozygous *MVK* variant or a heterozygous *TNFRSF1A* variant, highlighting the potential for misclassification and the need for comprehensive genetic evaluation in atypical cases. This overlap illustrates a broader challenge in autoinflammatory disease classification, where genetic and phenotypic spectra intersect.[72]

Collectively, these findings underscore that FMF genetics cannot be interpreted in isolation but must be considered within the interconnected network of autoinflammatory pathways.[64] They highlight the multilayered nature of FMF genetics, encompassing classical *MEFV* variants, modifier genes, epigenetic regulation, and overlapping disease genes that together shape the clinical phenotype.

Emerging concepts: somatic mosaicism

The advent of next-generation sequencing (NGS) has broadened the spectrum of *MEFV* variants, enabling the detection of rare and novel alleles as well as cases of somatic mosaicism, which have been increasingly reported in other autoinflammatory disorders, including CAPS (*NLRP3*) and VEXAS (*UBA1*).[73-75] A particularly emerging area of interest is somatic *MEFV* variants.[76] Although uncommon, somatic mosaicism has been proposed as a contributor to late-onset or atypical FMF, especially in cases where conventional germline testing fails to account for the phenotype. Somatic pathogenic variants may function similarly to low-penetrance germline alleles, modulating disease onset and severity; however, their detection requires high-depth sequencing methods that are not routinely applied in clinical practice. Current evidence remains limited, and further studies are required to clarify their role in FMF pathogenesis and clinical heterogeneity.

Diagnostic strategies in clinical practice

Genetic testing for FMF follows a stepwise, sequencing-based approach that balances efficiency with diagnostic accuracy. In patients from high-prevalence populations presenting with classical FMF symptoms, the first step typically involves targeted genotyping panels covering the most common founder variants, including p.M694V, p.M680I, p.V726A, and p.M694I. If these tests are negative or identify only a single heterozygous variant, Sanger sequencing of exon 10—where the majority of pathogenic variants cluster—is recommended.

When results remain inconclusive, particularly in atypical presentations or in populations with broader allelic heterogeneity, NGS multigene panel sequencing targeting genes associated with autoinflammatory diseases is indicated. NGS enables identification of rare or novel *MEFV* variants and helps exclude alternative autoinflammatory disorders when multigene panels are applied. Whole-exome or whole-genome sequencing may be justified in unresolved cases, although these approaches frequently reveal variants of uncertain significance. In select cases, especially adult-onset disease with atypical features, high-depth sequencing to detect somatic mosaicism may be considered in research or specialized clinical settings.

At each stage, careful interpretation using reference databases such as Infevers, combined with clinical scoring systems, is essential to avoid overcalling benign polymorphisms as pathogenic. This diagnostic pathway emphasizes that genetic findings must always be interpreted in the context of clinical presentation, a principle central to modern rheumatology genetics.

EPIGENETIC REGULATIONS IN FAMILIAL MEDITERRANEAN FEVER

The Genotype–phenotype gap

The existence of patient groups whose genotypes do not conform to the classical autosomal recessive model of FMF has prompted investigation into additional contributors to disease expression. Such groups include:

Patients carrying only a single pathogenic variant.[77,78]

Patients without any identifiable pathogenic variant.[79]

Healthy individuals harboring two pathogenic variants.[78]

Populations with the same ethnic background exhibiting different disease courses across countries.[80-82]

These observations have directed attention toward epigenetic regulation as a potential modifier of FMF pathogenesis. Epigenetic mechanisms alter gene expression without changing the underlying DNA sequence.[83] They encompass biochemical processes such as acetylation, methylation, and ubiquitination, as well as posttranscriptional regulation mediated by microRNAs (miRNAs).[83]

DNA methylation and chromatin architecture

Several studies have evaluated the methylation status of the *MEFV* gene and reported increased methylation,[84-86] particularly in exon 2, accompanied by reduced *MEFV* expression in FMF patients. Kirectepe et al.[84] demonstrated a negative correlation between *MEFV* methylation levels and gene expression. Similarly, Zekry et al.[86] reported that higher *MEFV* methylation was associated with increased disease severity. Erdem et al.[85] investigated the functional consequences of exon 2 methylation and identified alternative splicing of this exon as a key outcome. Furthermore, they observed altered subcellular localization of pyrin lacking exon 2, which localized predominantly to the cytoplasm rather than the nucleus, suggesting a potential mechanism for FMF in the absence of pathogenic variants.

Beyond *MEFV*-specific changes, global DNA methylation patterns in FMF patients have been assessed. Caldiran et al.[87] reported increased global methylation levels in FMF patients, with a positive correlation between global methylation and disease severity. They also demonstrated reduced expression of the *NLRP13* inflammasome, attributable to hypermethylation of its promoter region. Notably, FMF patients with amyloidosis exhibited higher *NLRP13* methylation than both FMF patients without amyloidosis and healthy controls, suggesting that this epigenetic alteration may contribute to amyloidogenesis and could merit screening in FMF patients.

Caldiran et al.[88] reported increased methylation of specific histone marks in FMF patients. These modifications reflected a combination of proinflammatory and anti-inflammatory influences, which the authors interpreted as indicative of heightened inflammatory activity accompanied by a compensatory regulatory response.

More recently, Röring et al.[89] assessed chromatin accessibility in FMF patients compared with healthy controls using ATAC-sequencing. They found that FMF patients exhibited a greater number of regions with reduced chromatin accessibility, particularly near genes involved in cellular regulatory processes. Integration with transcriptomic data, which demonstrated downregulation of immune-related pathways, suggested that these chromatin changes may represent a compensatory mechanism aimed at counterbalancing the chronic hyperinflammatory state observed in FMF.

Posttranscriptional regulation: microRNAs (miRNAs)

In a study examining demethylation of inflammasome-associated genes in autoinflammatory disorders, Vento-Tormo et al.[90] reported no significant differences between FMF patients and healthy controls. This outcome may reflect study limitations, including a very small FMF sample size (n = 5) and the fact that most patients (60%) were receiving anti–IL-1 therapy. Larger studies with appropriate adjustment for such confounders are therefore warranted.

MicroRNAs (miRNAs), small non-coding RNAs that regulate gene expression posttranscriptionally,[91] represent another major epigenetic mechanism studied in FMF. Multiple studies have consistently reported altered miRNA expression in FMF patients compared with healthy controls.[92-101] Differences have also been observed across clinical and genetic subgroups. For instance, Akkaya-Ulum et al.[92] reported distinct inflammatory miRNA profiles among homozygous patients, heterozygous patients, and healthy carriers, while Kahraman et al.[101] observed differential expression of specific miRNAs between homozygous and heterozygous individuals. Wada et al.[100] further demonstrated variation according to genotype and exon-specific mutations. Several studies also reported differential miRNA expression based on disease severity[97] and attack status.[99] Additionally, Tümerdem et al.[98] identified miRNAs targeting the *NFKB* and *NR3C* pathways that were differentially expressed in colchicine-resistant versus colchicine-responsive patients.

Several studies have investigated the functional role of miRNAs in FMF using advanced experimental approaches. Akkaya-Ulum et al.[102] demonstrated that miR-197-3p, previously reported as downregulated in FMF, exerts anti-inflammatory effects in functional assays. Using 3′UTR luciferase experiments, they identified IL-1R as a direct target of this miRNA and proposed that reduced miR-197-3p expression may contribute to FMF pathogenesis.

Similarly, Akbaba et al.[103] reported downregulated expression of miR-30e-3p in FMF patients. Functional transfection assays suggested its anti-inflammatory role, and 3′UTR luciferase and Western blot analyses identified IL-1β as a direct target. These findings indicate that miR-30e-3p could serve as a potential diagnostic and therapeutic marker in FMF.

Koga et al.[104] reported significantly reduced levels of miR-204-3p in FMF patients during attacks. Lipopolysaccharide stimulation similarly suppressed miR-204-3p in macrophages, and its inhibition increased TLR4-related cytokine production. Bioinformatics analyses suggested that miR-204-3p targets genes involved in the TLR pathway via regulation of PIK3γ, which was confirmed by luciferase assays demonstrating that miR-204-3p suppresses PIK3γ. Transfection of FMF monocytes further showed that miR-204-3p inhibition increased IL-6 and IL-12p40 expression. The authors proposed miR-204-3p as a potential diagnostic and therapeutic target in FMF.

Latsoudis et al.[105] reported that miR-4520a expression is significantly elevated in MEFV-variant carriers compared with healthy controls. *In silico* analyses suggested that miR-4520a negatively regulates autophagy-related genes via the RHEB/mTOR pathway. These findings are consistent with protein-level studies demonstrating impaired autophagy in FMF patients.[44-46]

Limitations and future perspectives

Despite significant advances in understanding epigenetic regulation in FMF, several key gaps remain. Existing studies have not established causal links between epigenetic alterations and *MEFV* pathogenic variants, nor have they clearly demonstrated their impact on clinical phenotype. Furthermore, confounding factors such as colchicine treatment, inflammatory status, and tissue specificity complicate the interpretation of current epigenetic data.

Prospective studies with larger cohorts and concordance analyses are therefore needed to delineate the phenotypic consequences of epigenetic modifications. A clearer understanding of these mechanisms may ultimately provide opportunities for the development of targeted therapeutic strategies, as well as improved diagnostic and prognostic tools in FMF.

CONCLUSION

FMF is the prototypical monogenic autoinflammatory disease, arising from pathogenic variants in the *MEFV* gene. Although it is well established that these variants lead to overactivation of the pyrin inflammasome and a resultant hyperinflammatory state, the precise mechanisms underlying this overactivation remain incompletely understood. Evidence from the literature suggests that alterations in pyrin ligand-binding activity, particularly within the B30.2 and CHS domains, together with disruptions in cytoskeletal regulation, constitute key pathogenic events in FMF. These alterations, which affect the same stage of pyrin inflammasome activation and produce similar downstream consequences, are likely interrelated components of a unified pathogenic mechanism.

While pathogenic *MEFV* variants are central to FMF, incomplete penetrance and variable clinical expression reflect additional layers of genetic and epigenetic regulation. In patients with atypical clinical features, pathogenic variants in other autoinflammatory genes should be considered. Current studies on epigenetic regulation in FMF remain insufficient to fully explain their impact on disease pathogenesis and phenotypic variability, highlighting the need for

rigorously designed investigations. A deeper understanding of these regulatory mechanisms has the potential to improve diagnostic accuracy, guide personalized therapeutic strategies, and inform prognosis in FMF patients.

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